PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants	: Kenneth H. Grabstein et al.
Application No.	: 09/724,841
Filed	: November 28, 2000
For	: POLYNUCLEOTIDES ENCODING EPITHELIUM-DERIVED T-CELL FACTOR AND USES THEREOF
Examiner	: Prema Maria Mertz
Art Unit	: 1646
Docket No.	: 66033-10/2811-H
Date	: October 4, 2006

Attention: Board of Patent Appeals and Interferences
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF (37 C.F.R. § 41.37)

Commissioner for Patents:

Appellants appeal from the final rejection of claims 20-30, 34, 35 and 41-45 of the above-identified application. This Brief on Appeal is submitted in response to the Office Action of July 7, 2006, rejecting the claims. The appeal is proper because the claims have been rejected twice.

The fees required under Section 1.17(c) are dealt with in the accompanying transmittal letter.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Amgen Incorporated, a Delaware corporation, which has its principal place of business at One Amgen Center Drive, Thousand Oaks, CA 94608.

II. RELATED APPEAL AND INTERFERENCES

No other appeals or interferences will directly affect, be affected by, or have a bearing on the Board of Patent Appeals and Interferences' decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-19, 31-33, and 36-40 were previously cancelled. Claims 20-30, 34, 35 and 41-45 stand rejected and are the claims on appeal. No other claims are pending.

IV. STATUS OF AMENDMENTS

In a Response filed on May 15, 2006, Appellants amended claims 20 and 41. The claims as shown in the accompanying Appendix are an accurate representation of the pending claims. The status of the prior amendments is relevant to the analysis of the current grounds of rejection on appeal, and is therefore summarized below for the Board's convenience.

Office Action mailed January 8, 2003. The Examiner stated that claims 20-30 were allowable if the pending rejections were overcome, and no prior art rejections were made.

Appellants' response mailed April 3, 2003. Claims 20-25 were amended to be free of the language objected to by the Examiner.

Office Action mailed June 12, 2003. The Examiner indicated that the rejection of claims 20-30 under 35 U.S.C. § 112, first paragraph, and of claims 20-25 under 35 U.S.C. § 112, second paragraph (in reference to "consisting essentially of") were withdrawn. Other rejections based on specific claim language were maintained, and the action was made final.

Amendment after final filed on December 1, 2003. The claim language was amended to address the remaining grounds of rejection.

Advisory Action mailed December 24, 2003. The Examiner stated that claims 20-30 were allowed. Claims 36-40 were rejected in view of the "moderate stringency" language. Therefore based on the status of the case as of December 24, 2003, Appellants reasonably believed that by canceling claims 36-40, claims 20-30 could proceed to issue.

Request for Continued Examination (RCE) filed on February 5, 2004. This RCE was filed just six weeks after Appellants received notice that claims 20-30 were allowed. Claims 36-40, the only previously rejected claims, were canceled by amendment.

Office Action mailed March 31, 2004. Despite being allowed just three months earlier, claims 20-30 were rejected on numerous grounds, including 35 U.S.C. § 112,

first paragraph (written description); 35 U.S.C. § 112, second paragraph (indefiniteness), and for the first time, 35 U.S.C. § 102(b) over a prior art reference, with no indication why the reference published in 1991 was not cited in the parent application.

Response filed June 30, 2004. Appellants filed a response to address all these issues, by argument and amendment. Appellants further amended the claims using language suggested by the Examiner in the March 31, 2004 Office Action. In this response, Appellants also summarized the prosecution history, with a discussion of the previous allowance of claims 20-30.

Office Action (Final) mailed August 9, 2004. The Action contained new (despite the finality) 35 U.S.C. § 112, first paragraph, rejections, and the previous rejections were maintained.

Response filed on December 8, 2004. Arguments and amendments were filed to address the new and previous grounds of rejection.

Advisory Action mailed December 21, 2004. The Examiner did not enter the amendment, solely on the grounds that an amendment (with an obvious typographical error, SEQ ID NO:12 instead of SEQ ID NO:13, that the Examiner should have recognized) to overcome the prior art raised an issue of new matter.

Summarizing this extensive history of claim amendments, Appellants submit that the Examiner erred when she failed to abide by her previous indication that claims 20-30 were allowable, and failed to allow the case to go to issue when Appellants canceled all the remaining rejected claims on February 5, 2004. It is unclear why claims 20-30, which were allowed on December 24, 2003, became subject to numerous grounds of rejection just three months later. No reason was given that would justify this, such as a relevant change in the law.

Meanwhile, the Court of Appeals for the Federal Circuit has now issued clear guidelines for evaluating written description in the area of polynucleotide claims. In *Capon v. Eshhar,* Slip. Op. 03-1480, -1481 (Fed. Cir. August 12, 2005), case law that this Examiner previously cited in the Office Action dated August 9, 2004, was found not to be controlling precedent under facts that, as argued below, Appellants believe are analogous to the present claims.

Applicants filed a Brief on Appeal on January 18, 2006, and the Examiner issued a new non-final Office Action on March 2, 2006. The rejection of claims 41-45 under 35 U.S.C. § 112, first paragraph, was maintained, as was the rejection of claims 20-30, 34-35, and 41-45 under 35 U.S.C. § 112, second paragraph.

Claims 20, 26, 30, 34 and 35 were again rejected under 35 U.S.C. § 102(b) as being anticipated by Smith *et al.*

On May 15, 2006, applicants filed a response addressing the rejections. Claim 20 was amended to address the rejection under 35 U.S.C. § 112, second paragraph, and claim 41 was amended to address the 35 U.S.C. § 112, first paragraph, rejection. A final Office Action was mailed on July 7, 2006. 35 U.S.C. § 112, first paragraph (written description) and second paragraph rejections were asserted, and the rejection under 35 U.S.C. § 102(b) over Smith was maintained.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to a mammalian epithelium-derived T-cell factor, now referred to as IL-15. Appellants discovered and sequenced a nucleic acid that encodes IL-15, and also prepared polypeptides that stimulate proliferation and differentiation of T-lymphocytes.

As described in the specification, one use of the protein is to promote long-term *in vitro* culture of T-lymphocytes and T-cell lines. (Page 6, lines 5-8.) In particular, purified protein (referred to as rETF, for recombinant Epithelium-Derived T-cell Factor) stimulated *in vitro* proliferation of CTLL-2 cells. (Example 6, page 40, lines 1-17.) The protein also induced cytotoxic T-lymphocyte lytic activity, lymphokine activated killer cell activity, and natural killer cell activity in human peripheral blood mononuclear cells.

These activities have important ramifications for treating diseases that involve T-cell activity. For example, natural killer T-cells play a role in destroying tumor cells and virus-infected cells in the body. Using the protein of the invention to stimulate T-cells will expand the population of cells that destroy tumor cells and will also be instrumental in destroying virus-infected cells. (Page 45, lines 6-15.) Independent claim 20 is supported at page 26, lines 27-34 and page 3, lines 16-23, and recites an isolated nucleic acid selected from the group consisting of (a) a nucleic acid of at least 12 contiguous nucleotides of SEQ ID NO:1; (b) a nucleic acid of at least 12 contiguous

nucleotides of SEQ ID NO:4; (c) a nucleic acid of at least 12 contiguous nucleotides complementary to SEQ ID NO:1, and (d) a nucleic acid of at least 12 contiguous nucleotides complementary to SEQ ID NO:4 wherein said isolated nucleic acid of (a) or (b) is capable of specifically binding to the complement of the polynucleotide of SEQ ID NO:1 or SEQ ID NO:4, respectively; and the nucleic acid of (c) or (d) is capable of specifically binding to the polynucleotide of SEQ ID NO:1 or SEQ ID NO:4, respectively.

The claims on appeal relate to several aspects of the invention. Dependent claims 21-30, 34 and 35 provide isolated polynucleotides of various lengths having contiguous nucleotides from polynucleotides of the invention. In certain embodiments, the polynucleotide is claimed as part of a composition (claim 30). In other embodiments (claim 34) the nucleic acid is DNA or RNA. Claims 20-30, 34 and 35 all refer to polynucleotide aspects of the invention, meaning material that either encodes IL-15, or can be used as a probe to detect a polynucleotide encoding IL-15. These embodiments are described throughout the specification, particularly at page 26, lines 19-36 and page 27, lines 1-8 and 24-30.

Independent claim 41 recites an oligonucleotide of at least 14 nucleotides in length capable of forming a stable duplex with nucleic acid which encodes a polypeptide of SEQ ID NO:3 or SEQ ID NO:6. The dependent claims, 42-44, relate to the invention as described at page 12, lines 14-22, and recite oligonucleotides of at least 14 nucleotides in length capable of binding to mRNA encoding IL-15, or to the related cDNA sequences. Dependent claim 45 represents a particular embodiment in which the oligonucleotide is part of a composition also comprising a pharmaceutically acceptable diluent or carrier.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Did the Examiner err by rejecting claims 41-45 under 35 U.S.C. § 112, first paragraph, for alleged failure to comply with the written description requirement, because the specification does support oligonucleotides as claimed that can form a stable duplex?

II. Did the Examiner err by rejecting claims 20-30 and 34-35 under 35 U.S.C. § 112, second paragraph, for indefiniteness, because the claims do recite definite subject matter?

III. Did the Examiner err by reject claims 20, 26, 30 and 35 under 35 U.S.C. § 102(b) as being anticipated by Smith *et al.*, because the nucleic acid of the reference would not bind as recited in the claims?

VII. ARGUMENTS

I. Did the Examiner err by rejecting claims 41-45 under 35 U.S.C. § 112, first paragraph, for alleged failure to comply with the alleged failure to comply with the written description requirement, because the specification does support oligonucleotides as claimed that can form a stable duplex?

In the Office Action dated March 2, 2006, the Examiner stated that to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors cited by the Examiner include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. However, no case law or precedent was cited for these factors.

The Examiner stated that there is allegedly no written description for claims drawn to a genus of polynucleotides that hybridize under conditions of moderate stringency to a nucleic acid which encodes a polypeptide comprising SEQ ID NO:3 or 6.

The Examiner further stated that recitation of "high stringency" in claim 41 would not have obviated the rejection without reciting the conditions. Claims 41 recites the language of the specification at page 27, lines 24-30, wherein the sequences are "highly specific" and form "stable duplexes" with the target sequence. The sequences as described do not form duplexes with other regions of DNA. Applicants argued that claim 41 as amended obviated the rejection, and as claims 42-45 depend from claim 41, the rejection of claims 41-45 should be withdrawn.

In the Office Action dated July 7, 2006, the Examiner maintained the rejection and stated that applicants have not provided written description for which oligonucleotides can form a stable duplex, because there is allegedly no functional together with structural language in with respect to the nucleic acid that also forms the stable duplex.

Appellants submit that the specification clearly describes the genus of oligonucleotide molecules that fall within the scope of the claims. The following written description is found at page 27, lines 24-28 of the specification:

> Primers for the amplification of a selected sequence should be selected from sequences which are highly specific and form stable duplexes with the target sequence. The primers should also be non-complementary, especially at the 3' end, should not form dimers with themselves or other primers, and should not form secondary structures or duplexes with other regions of DNA. (Emphasis added)

Thus, the specification does provide written description for oligonucleotides that form stable duplexes with SEQ ID NO:1 or SEQ ID NO:4.

II. Did the Examiner err by rejecting claims 20-30 and 34-35 under 35 U.S.C. § 112, second paragraph, for indefiniteness, because the claims do recite definite subject matter?

The Examiner stated in the Office Action of July 7, 2006, that claim 20(c)-(d) is vague and indefinite because the at least 12 contiguous nucleotides could be attached to "totally unrelated nucleotides." (Office Action, p. 4, ll. 8-9.)

Appellants disagree, because claim 20 clearly recites that the nucleic acid of (c) or (d) is capable of specifically binding to the polynucleotide of SEQ ID NO:1 or SEQ ID NO:4, respectively. A nucleic acid would not be able to specifically bind to SEQ ID NO:1 or SEQ ID NO:4 if it was attached to a totally unrelated nucleotide, because that attachment could destroy the specificity.

III. Did the Examiner err by rejecting claims 20, 26, 30, 34 and 35 under 35 U.S.C. § 102(b) as being anticipated by Smith *et al.*, because limitations in dependent claim 20 place it and the remaining dependent claims beyond the scope of this rejection?

In the Office Action of July 7, 2006, the Examiner stated at page 5, lines 1-7,

> Applicants have provided no evidence that the identical 12 nucleotides in common in the Smith reference will not specifically bind to the complement of SEQ ID NO:1. Those of skill in the art would expect the specific binding of the 100% identical nucleotides 1-13 of SEQ ID NO:1 and

> ATGAGAATTTCGA of the reference. The prior art nucleic acid would inherently have the capability of specifically binding to the polynucleotide of SEQ ID NO:1. There is enough complementarity for the prior art nucleic acid to specifically bind to the polynucleotide of SEQ ID NO:1 under the right conditions.

The Examiner further agreed that Smith does not teach an isolated oligonucleotide ATGAGAATTTCGA, but stated that the claim does not recite such. The Examiner concluded at page 6, lines 3-5,

> In the absence of the recitation of "fully complementary to SEQ ID NO:1," the nucleic acid of the reference would specifically bind to the polynucleotide of SEQ ID NO:1.

Appellants submit that this is in error. Smith discloses, as the Examiner admits, a polynucleotide of 592 nucleotides, which encodes a cellular retinol binding protein unrelated to the IL-15 of the invention. Appellants fail to understand how a 592-nucleotide cellular retinol binding protein polynucleotide could specifically bind to a polynucleotide of SEQ ID NO:1 or SEQ ID NO:4, as clearly recited in claim 20 and thereby in dependent claims 26, 30, 34 and 35.

In order for a reference to anticipate a claim, "a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 U.S.P.Q. 2d 1565, 1567 (Fed Cir. 1995). Smith discloses mouse cellular retinol binding protein (CRBP) cDNA in Figure 1(A). There is no evidence of record that mouse CRBP cDNA will specifically bind to SEQ ID NO:1, SEQ ID NO:4, or the complements thereof. The ATGAGAATTTCGA embedded within CRBP cDNA is but a tiny part of the full length cDNA and it does not exist without the flanking sequence. It only exists as information. It does not exist as a polynucleotide that falls within the scope of the claims.

Claim 20 requires that the nucleic acid be (1) isolated; and (2) specifically bind to a polynucleotide of SEQ ID NO:1 or 4, or the complements thereof. Smith fails to meet either of these limitations. The Smith ATGAGAATTTCGA sequence is not isolated, and in its present form it does not specifically bind to a polynucleotide of SEQ ID NO:1 or 4, or the complements thereof.

In other words, the Smith reference does not disclose a 12 nucleotide portion of a nucleic acid. The reference teaches a polynucleotide of 592 nucleotides. This polynucleotide would not specifically bind or form a stable complex in the manner required by the claims. Smith does not call out or teach the oligonucleotide ATGAGAATTTCGA. In fact, this oligonucleotide is within a larger underlined sequence used for screening; see legend to Figure 1(A) at page 2224 of Smith. According to Smith, the ATGAGAATTTCGA noted by the Examiner would be flanked by enough bases to prevent stable duplex formation with the polynucleotides recited in the present claims.

Smith does not teach an isolated oligonucleotide of ATGAGAATTTCGA. Furthermore, Smith represents a different protein art (cellular retinol binding protein) and one of skill would not look to a cellular retinol binding protein for teaching of an oligonucleotide capable of specifically binding to IL-15. The use of the Smith reference is a construct of electronic sequence searching and bears no relationship to real life anticipation in the art.

The Examiner stated on previous occasions (Office Action mailed January 8, 2003; Advisory Action mailed December 24, 2003) that claims 20-30 were not subject to prior art rejections and were allowable or allowed. Appellants submit that the 1991 Smith reference is an anomaly of database searching and does not represent true anticipatory art because the twelve nucleotide sequence is not isolated, and instead is embedded within a much longer sequence. The reference fails to teach isolation of the cited sequence, and it teaches no function whatsoever outside the cellular retinol binding protein.

Commissioner is hereby authorized to charge the required Appeal fee of $500, to Deposit Account No. 04-0258. If additional fees are believed necessary, the Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

Respectfully submitted,
Kenneth H. Grabstein et al.
DAVIS WRIGHT TREMAINE LLP

By _____
Jane E. R. Potter
Registration No. 33,332

Enclosures:
Postcard
Form PTO/SB21
Two copies of this Brief

2600 Century Square
1501 Fourth Avenue
Seattle, WA 98101-1688
Phone: (206) 628-7650
Facsimile: (206) 628-7699

VIII. APPENDIX OF CLAIMS INVOLVED IN THE APPEAL

20. An isolated nucleic acid selected from the group consisting of (a) a nucleic acid of at least 12 contiguous nucleotides of SEQ ID NO:1; (b) a nucleic acid of at least 12 contiguous nucleotides of SEQ ID NO:4; (c) a nucleic acid of at least 12 contiguous nucleotides complementary to SEQ ID NO:1, and (d) a nucleic acid of at least 12 contiguous nucleotides complementary to SEQ ID NO:4 wherein said isolated nucleic acid of (a) or (b), is capable of specifically binding to the complement of the polynucleotide of SEQ ID NO:1 or SEQ ID NO:4, respectively; and the nucleic acid of (c) or (d) is capable of specifically binding to the polynucleotide of SEQ ID NO:1 or SEQ ID NO:4, respectively.

21. The nucleic acid of claim 20 which is 12 to about 75 contiguous nucleotides in length.

22. The nucleic acid of claim 20 which is 12 to 14 nucleotides in length.

23. The nucleic acid of claim 20 which is 14 to 18 nucleotides in length.

24. The nucleic acid of claim 20 which is 18 to 20 nucleotides in length.

25. The nucleic acid of claim 20 which is 20 to about 75 nucleotides in length.

26. The nucleic acid of claim 20 labeled with a radioactive, fluorescent, enzymatic, or chromogenic marker.

27. The nucleic acid of claim 20 wherein the nucleic acid is DNA.

28. The nucleic acid of claim 27 selected from the group consisting of (a) a nucleic acid consisting of SEQ ID NO:9; (b) a nucleic acid consisting of SEQ ID NO:10; (c) a nucleic acid consisting of SEQ ID NO:11; (d) a nucleic acid complementary to SEQ ID NO:9; (e) a nucleic acid complementary to SEQ ID NO:10; and (f) a nucleic acid complementary to SEQ ID NO:11.

29. The nucleic acid of claim 27 selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10, and SEQ ID NO:11.

30. A composition comprising the nucleic acid of claim 20 and a diluent or carrier.

34. The nucleic acid of claim 20 wherein the nucleic acid is DNA, or RNA.

35. The nucleic acid of claim 20 where the nucleic is RNA.

41. An oligonucleotide of at least 14 nucleotides in length capable of specifically forming a stable duplex with a nucleic acid which encodes a polypeptide comprising SEQ ID NO:3 or SEQ ID NO:6.

42. The oligonucleotide of claim 41 which is DNA or RNA.

43. The oligonucleotide of claim 41 which is DNA.

44. The oligonucleotide of claim 41 which is RNA.

45. A composition comprising the oligonucleotide of claim 41 and a pharmaceutically acceptable diluent or carrier.

IX. EVIDENCE APPENDIX

Pursuant to 37 C.F.R. § 41.37(c)(1)(ix) no evidence under 37 C.F.R. § 1.130. 1.131 or 1.132 is relied upon in this Appeal Brief.